

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED Final Report: 06/01/93-08/31/96
4. TITLE AND SUBTITLE Mechanisms of the Basal Ganglia for Arm-Hand Coordination		5. FUNDING NUMBERS Award No. N00014-93-1-0694
6. AUTHOR(S) Michael A. Arbib		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Computer Science Department University of Southern California Los Angeles, CA 90089-2520		8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Office of Naval Research - AASERT Attn: Teresa McMullen 800 North Quincy Street Arlington, VA 22217-5660		10. SPONSORING/MONITORING AGENCY REPORT NUMBER
11. SUPPLEMENTARY NOTES n/a		
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release: Distribution unlimited		12b. DISTRIBUTION CODE

3. ABSTRACT (Maximum 200 words)

The basal ganglia (BG) appears to play a dual role in the performance of voluntary movements: 1) the direct path is primarily involved in providing an estimate of next sensory state to the cortex, and 2) the indirect path is mainly responsible for the inhibition of movement while the cortex is either involved in choosing the next motor command for execution, or while waiting for a "go" signal to indicate the end of a delay period. Its strong ties with the supplementary motor area (SMA), a region involved with planning sequential movements, suggest the basal ganglia assists in movement planning and performance by providing the SMA with information regarding the expected state, such that SMA may begin planning the next sequence of the behavior. Disruption of normal motor function, such as that seen in Parkinson's disease, demonstrates a difficulty in performing sequential movements, with some patients exhibiting slower movement or a pause between sequences. This may be attributed to the indirect pathway, which prevents the next sensory state from reaching the cortex, thus inhibiting it from preparing to execute the next movement in a sequence. A computer model of neural networks involved in arm movement was developed to demonstrate the suggested relationship between the two pathways.

14. SUBJECT TERMS HIGH QUALITY INDEXED 3		15. NUMBER OF PAGES
		16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified
		20. LIMITATION OF ABSTRACT UL

**FINAL REPORT
OFFICE OF NAVAL RESEARCH
800 NORTH QUINCY STREET
ARLINGTON, VA 22217-5660**

Principal Investigator: Michael A. Arbib
Institution: University of Southern California
Project Title: Mechanisms of the Basal Ganglia for Arm-Hand Coordination

Published Abstracts

Bischoff, A., Arbib, M. A., and Winstein, C. J., 1996, A Computational Model of the Role of Basal Ganglia in a Reciprocal Aiming Task, *Society for Neuroscience Abstracts*, 22:2028.

Papers in Preparation

Bischoff, A., Arbib, M. A., and Winstein, C. J., A Working Model of the Basal Ganglia in the Performance of a Reciprocal Aiming Task.

Crowley, M., Bischoff, A., and Arbib, M. A., Basal Ganglia Function: Sensory Expectations and the Suppression of Unwanted States.

Presentations

“Modeling the Basal Ganglia”, HFSP Meeting: From Attention to Action, Lyon, France, October 3-5 1994.

In: Society for Neuroscience Abstracts (1996), 22:2028.

A COMPUTATIONAL MODEL OF THE ROLE OF BASAL GANGLIA IN A RECIPROCAL AIMING TASK. A. Bischoff*, M.A. Arbib, and C.J. Winstein. University of Southern California, Los Angeles, CA 90089-2520.

A rapid reciprocal aiming task was used to test performance of arm movement in control subjects and in Parkinson's disease patients (Winstein and Pohl, 1995; Winstein et al., 1995). Targets were 37 cm apart with a width of either 8 cm or 2 cm. Parkinson's patients demonstrated a slower movement time and exhibited less variance in movements than controls. A computational model of the basal ganglia demonstrated that a reduction in the disinhibition of the ventrolateral thalamus by the internal globus pallidus may produce the slower velocity by the lack of drive to the motor cortex and the supplementary motor area (SMA). A simulated three-jointed arm was used to study the arm movements, with the motor cortex providing velocity and positional information. The aiming task was treated as a sequence of movements, with the supplementary motor area responsible for the overall sequence. The basal ganglia, with its strong pallidothalamic projections to SMA-proper, is proposed to assist in the sequencing of movements by inhibiting other motor control programs while permitting the current movement of the sequence to be performed. The weaker disinhibition therefore causes a difficulty not only in performing the current movement, but in setting up the next movement of the sequence as well. As seen with the Parkinson's patients, the parkinsonian version of the model was more restricted in its tapping placement on the targets than when functioning as a control subject. The model also supports Fitts' Law, which states that task complexity increases with larger distances and smaller target widths.

Supported in part by a grant from the Human Frontier Science Program and by AASERT award N00014-93-1-0694 from the Office of Naval Research.

A Working Model of the Basal Ganglia in the Performance of a Reciprocal

DRAFT
9/30/96
Introduction

Aiming Task

A. Bischoff, M. A. Arbib, and C. J. Winstein

Parkinson's disease is a well-known affliction of the basal ganglia. It has several striking symptoms, including a shuffling gait, akinesia, bradykinesia, rest tremor, and a difficulty in the performance of sequential tasks. Parkinson's patients often perform movements more slowly, and appear to have some difficulty in the initiation of movements as well. What causes these motor performance difficulties? Given that the disease is characterized by cell death within the substantia nigra and therefore a depletion of dopamine within the striatum, it is possible that the loss of dopamine results in a lack of drive from the basal ganglia. Another theory is that slow movement is a result of tremor.

More recently, it has been suggested that the basal ganglia is involved in two tasks, namely, the inhibition of motor activity and the estimation of the next sensory state (Crowley et al., in preparation).

- Expand on above theories.
- Review CBA paper.
- See lit on tremor/rigidity in PDs. Downloaded refs are found in Norris and UCLA libraries. Staude has done several studies on tremor and PDs, one suggesting that motor initiation is related to tremor, and a more recent study suggesting movement time is correlated with tremor.

The Aiming Task

A rapid reciprocal aiming task was used to test performance of arm movement (Winstein & Pohl, 1995). In this task, the subject was asked to perform 3 different behaviors: 1) stylus tap on a single 8 cm wide target; 2) stylus tap between two 8 cm wide targets located 37 cm apart; and 3) stylus tap between two 2 cm wide targets located 37 cm apart. Each task required the participant to perform as fast and as accurately as possible over a 10 second period. The task was performed by right-handed control subjects, left and right hemisphere stroke victims (Winstein and Pohl, 1995), and by Parkinson's patients both "on" and "off" levadopa treatment (Winstein et al., 1995). The tasks correlate well to work by Paul Fitts (1954), who determined that task complexity increased with larger movement distances and smaller target widths,

$$ID = \log_2(2A/W)$$

where ID is the index of difficulty, A is the movement distance, and W the target width. In general, low ID condition (i.e., large target size) movement is primarily open-loop, a ballistic process not relying upon visual feedback for accuracy, while high ID conditions (i.e., small target size, greater distance) are governed by at least two processes: 1) an open-loop process controlling the ballistic phase which brings the end effector closer to the target, and 2) a closed-loop process which requires feedback as the end effector approaches the target point. Using Fitt's Law, the tasks have the following IDs: 1) stylus tap on a single target, ID = 0 (Low); 2) stylus tap

between two 8 cm wide targets, ID = 3.21 (Medium); and 3) stylus tap between two 2 cm wide targets, ID = 5.21 (High).

- What were results for normals, PDs?
- What does task signify?
- Why is it useful for modeling studies?

A Model of the Basal Ganglia

A model was designed to replicate the behavior seen in the aiming task, centering around the proposed role of the basal ganglia. The model assumes the basal ganglia plays a role in velocity via its feedback to the motor cortex. Essentially, the basal ganglia lack of inhibition on the thalamus during movement performance may be viewed as motivation towards completing the task. The lower the inhibition, the more motivation, allowing the motor cortex to perform higher velocity movements. This is seen in a PD patient's difficulty to perform self-initiated movements, or in needing motivational information in order to perform tasks as the disease progresses {##REF##}. Therefore, as the disinhibition of the thalamus is weakened in a dopamine-deprived basal ganglia, it is increasingly difficult for the motor cortex to drive the movement, and thus movement is performed at a slower velocity.

- Assume BG controls velocity, and on/off points. When BG is lost, we lose both drive (bradykinesia) and replace on/off by a more peripheral feedback role.
- On velocity -- check out work by Contreras-Vidal.
- Have each "neuron" represent a population. Given 10 neurons, have each neuron represent x degrees of movement, strength of firing could then represent velocity.

Premotor Cortex

- For each brain region, compare to CBA, and provide information as to its role within the model.

The premotor cortex is a cortical region bordering the arcuate sulcus and the motor cortex. Kurata (1994) divides it into at least two functionally distinct regions: dorsal premotor cortex (PMd), and ventral premotor cortex (PMv), located along the inferior limb of the arcuate sulcus. Functionally, PMd appears to contribute more to motor preparation by integrating neural programs needed for the intended action and execution of the behavior, while PMv may be more specialized for motor execution via visual guidance (Kurata, 1993). PMv receives thalamic projections, with caudal PMv (area F5) receiving predominantly from area X and VPLo, while rostral PMv (area F4) receives projections mainly from VLo (Matelli et al., 1989). PMd appears to receive afferents from VLo, indicating a possible relationship with the basal ganglia (Inase & Tanji, 1994). Since area F5 appears to be dominated by distal movements, while area F4 is more involved with proximal movements, and VLo is a pallidothalamic target, while VPLo and area X are cerebellothalamic targets, this suggests that distal movements are more heavily influenced by the cerebellum, while proximal movements are more basal ganglia influenced. Premotor cortex also has rich links with the supplementary area, such that SMA-proper is linked primarily with areas F2 and F4, and modestly with F5, while pre-SMA receives strong input from the anterior premotor areas (particularly F5), and weak inputs from F2 and F4 (Luppino et al., 1993).

Supplementary Motor Area

The supplementary motor area has only recently been split into two areas (Luppino et al., 1991; Matelli et al., 1991; Tanji, 1994): SMA-proper (F3), located rostral to the motor cortex (F1), and pre-SMA (F6), located rostrally to SMA-proper, to the anterior end of the agranular frontal cortex. SMA-proper has rich links with the motor cortex and with the posterior premotor and cingulate areas, while pre-SMA is strongly connected with anterior premotor, and cingulate area 24c, and exhibits no connections with the motor cortex (Luppino et al., 1993). In addition, VLo of the motor thalamus, which receives projections from the basal ganglia, projects strongly to SMA-proper, while area X, a cerebellar-receiving region, projects to pre-SMA (Rouiller et al., 1994). Functionally, it would appear that SMA-proper is more responsible for movement execution, while pre-SMA is more involved with the "high level" motor functions. For example, Mushiake et al. (1991) trained macaques to perform a sequential motor task in two different directions. The first condition was a visually triggered task, requiring the monkey to reach and touch three pads by following the lights illuminated behind the pads. The second condition required the monkey to remember a predetermined sequence and press three pads without any visual guidance. The results indicated that sequence specific neurons were more common within the SMA, while transition specific (neurons involved during the transitional phase, where the monkey learned to memorize the correct sequence) neurons were more likely within the premotor cortex. SMA's involvement with sequencing has more recently been supported by Tanji and Shima (1994), in which SMA-proper displayed neurons which were

preferentially active in relation to a particular order of forthcoming memory-guided movements. Other neurons displayed movement-related behavior (firing for a particular movement). In a conditional sequential motor task, Halsband et al. (1994) found that pre-SMA neurons were generally more active during the delay and premovement phases than for movement, instruction, and reward periods and was more active during the premovement phase of an externally triggered task, while SMA-proper was more active when the sequential task was internally generated. Tanji (1994) further suggests that SMA is important in tasks requiring memory retrieval, and in addition is important in the temporal organization of movements, particularly the sequencing of multiple movements.

Motor Cortex

The motor cortex (MC) appears to contain cells which discharge in relation to the next intended movement in a complex movement sequence, more commonly known as preparatory cells (Humphrey & Tanji, 1991). The movement fields of many MC neurons within the arm-hand region are restricted to movements about one or two contralateral joints. The neurons are sensitive to somatosensory input, even when no movement is involved; while few will respond to auditory or visual stimuli unless it is to trigger a motor response, they are still tightly coupled to response occurrence and to the stimulus. Cortical cells show a preferred direction of limb movement, with individual cells showing a broad tuning for a preferred direction, such that a population of these cells may command overall limb movement direction (Wise, 1993). This implies that a neuron may participate in

movements of various directions. Georgopoulos (1993) has suggested that a population vector may exist, in which the direction for reaching is a collection of these vectors, each representing the contribution of a directionally tuned cell. A vector points in the cell's preferred direction, and its length is proportional to the change in the cell's activity associated with a particular movement direction. The weighted sum of vectors would then approximately represent the direction of the ensuing movement. It has also been suggested that the discharge of MC cells is related to the force or torque about a given joint (Humphrey and Tanji, 1991).

In a study of motor cortex response via electrical stimulation of primate supplementary motor area and ventralis posterior lateralis pars oralis (VPLo) of thalamus, it was determined that the majority of neurons active during the preparatory period were active due to SMA stimulation, whereas movement related neurons (based upon increases in activity immediately before and during reaching movements) were activated by VPLo or SMA stimulation (Aizawa & Tanji, 1994).

PET studies have shown activation in motor cortex during delay phases of an experiment, in which no actual movement takes place (Kawashima et al., 1994). In addition, areas of motor cortex, premotor cortex and supplementary motor area appeared to generate new fields after learning of a pointing-in-sequence task. There has been evidence of neuronal activity in the motor cortex related to both actual movement, and preparatory activity (Alexander & Crutcher, 1990b; Kawashima et al., 1994). Kawashima et al. also reported what they felt was learning-dependent activity within the motor cortex.

Putamen

Globus Pallidus

The GABAergic projections of the putamen to the globus pallidus segments have been broken down into the direct (internal) and indirect (external) pathways (Alexander & Crutcher, 1990a; Alexander et al., 1990), thus suggesting two slightly different roles for these connections. The striatal output to the external globus pallidus may be responsible for suppressing the tonic inhibitory influence of GPe on the subthalamic nucleus and eventually increasing inhibition on the thalamus, while output to GPi assists in the disinhibition of the ventrolateral thalamus. It thus appears that these two pathways have opposing effects on the output of the basal ganglia itself. Excessive activity involving the indirect pathway leads to hypokinetic disorders, such as akinesia and bradykinesia, whereas excessive activity within the direct pathway produces hyperkinetic disorders, such as dyskinesia (DeLong, 1990). One interesting aspect of the striatopallidal projections, though, is that the matrisomes of the striatum appear to overlap their projections to both the internal and external globus pallidus (Flaherty & Graybiel, 1993). While only about 3% of the neurons within the matrisomes may project to both regions, typically over 70% of the neurons projected to the external region, compared to about 10% projecting to the internal globus pallidus. It has therefore been suggested by Flaherty and Graybiel (1993) that the matrisomal clustering may be coordinating signals sent to the direct and indirect pathways.

Pallidal neurons demonstrate a high rate of tonic activity, often firing rhythmically. GPe neurons appear to have two characteristic discharge patterns: high spontaneous discharge rates with pauses with a mean firing rate of 56 spikes/sec, or a low spontaneous discharge with occasional high frequency bursts, with a mean firing rate of just 9.6 spikes/sec (Mitchell et al., 1987). GPi neurons exhibit a high spontaneous discharge rate without pauses, with a mean firing rate of 71 spikes/sec (Mitchell et al., 1987). These firing rates change in relation to movement (DeLong et al., 1985). There is still some dispute, however, as to the relationship of the response to the overall movement. While evidence appears to correlate the direction of movement with neuronal activity (Brotchie et al., 1991a; Mitchell et al., 1987), there are conflicting results as to whether activity also relates to other movement parameters, such as amplitude and velocity, and response to load application. Brotchie et al. (1991a; 1991b) found only directional activity and suggest the basal ganglia provides the signal to the supplementary motor area as to the completion of a portion of a sequence, and Nambu et al. (1990) found evidence of neuronal discharge during the delay period of a go/no-go discrimination task, in addition to movement and visual stimulus-sensitive cells. This may imply that, rather than actual involvement in the performance of a movement, the basal ganglia is involved in the preparation to perform a movement, and in signaling its completion to the cortex in order to allow performance of the next sequence.

In Parkinson's disease, the loss of dopamine within the substantia nigra accounts for the various motor symptoms of tremor, akinesia, and rigidity. In studying MPTP models of parkinsonism, Bergman et al. (1994) found the striatal loss of

dopamine results in a reduction of tonic activity in GPe, thus producing disinhibition in the subthalamic nucleus and resulting overall in an excessive subthalamopallidal drive. This may result in tremor seen in both humans and primates inflicted with parkinsonism. Filion et al. (Filion et al., 1988) postulate the reduction in dopamine may reduce the selectivity while increasing the gain within the basal ganglia, such that the system responds to noise, based upon their study of passive limb movements in MPTP treated monkeys. The noise may then be responsible for rigidity, while high gain may produce the tremor. The selectivity problem may result in akinesia and the difficulty to perform complex, learned behaviors. This result is in agreement with Bergman et al. (1994), who believe that the abnormal phasic responses of the globus pallidus may result in tremor or akinesia.

Subthalamic Nucleus

The subthalamic nucleus appears to be somatotopically organized (Wichmann et al., 1994a), providing further evidence of pathway segregation believed to exist within the basal ganglia (Alexander et al., 1990; Hoover & Strick, 1993). Hamada and DeLong (1992a; 1992b) performed lesion studies on primate subthalamic nucleus to determine its role in the production of dyskinesia. They found that STN had excitatory glutamatergic projections to both GPe and GPi based upon the reduction in activity in both regions. They then theorized that a reduction in GPi activity facilitates cortically initiated movements via the disinhibition of thalamocortical neurons, whereas an increase in activity may stabilize or reduce/prevent competing

movements due to an increase of inhibition of the thalamus. It was also noted that an overactive subthalamic nucleus produced hypokinetic disorder, while an underactive STN produced hyperkinetic disorder. Based upon the finding of a late onset response during a step tracking task (Wichmann et al., 1994a), STN's involvement in the indirect pathway may suggest a role in ongoing movements, rather than in the initiation or selection of movement. In MPTP-treated monkeys, an increase in tonic and phasic activity in STN and GPi was found, producing an increase in inhibition of thalamocortical neurons by GPi, which may cause the akinesia and rigidity seen in Parkinson patients (Bergman et al., 1994; Wichmann et al., 1994b). Tremor may be the result of a periodic oscillation in activity in the cortico-STN-GPi-thalamic pathway. Lesioning globus pallidus or the subthalamic nucleus in rats also affected nigrothalamic response to cortical stimulation (Ryan & Sanders, 1994).

Thalamus

The anterior ventrolateral nucleus of the thalamus (VLa) is believed to receive inhibitory projections from the internal segment of the globus pallidus and project to the supplementary motor area (Forlano et al., 1993). While controversy over projections to motor cortex still exists, Holsapple et al. (Holsapple et al., 1991) reported projections to the hand area of motor cortex, to areas different from portions of thalamus believed to receive projections from the cerebellum. This appears to support the theory that the basal ganglia and cerebellum send segregated projections within the cortex. During a paradigm involving wrist movement,

Forlano et al. (1993) reported while neurons in VLa tended to have directional preferences, few cells reacted to passive movement, somatosensory stimuli, or showed activity in relation to movement amplitude, velocity, or joint position. This lends credence to the belief that the globus pallidus is more involved with preparation of movement (Brotchie et al., 1991a) rather than initiating the movement itself (Mitchell et al., 1987).

Another area of thalamus receiving pallidal projections is the ventrolateral pars oralis (VLo), an area which also appears to project to motor cortex (Holsapple et al., 1991). Vitek et al. (1994) studied the physiological behavior of a number of thalamic regions, including VLo and VPLo, the ventralis posterior lateralis pars oralis, an area receiving projections from the cerebellum. VLo exhibited a strong somatotopic organization and closely packed neurons, with a longer latency and smaller amplitude response than did VPLo in a torque-induced passive displacement experiment. This suggested that VPLo's response was short enough to act as a relay to the motor cortex of proprioceptive information. VLo's more active movement response may not be involved in correction of movement (as hypothesized to be initiated by the cerebellum) but rather in the preparation or planning of the movement. In a multiple tracing study, Rouiller et al. (Rouiller et al., 1994) found that motor cortex did receive projections from both VLo and VPLo, but were unclear as to whether cells within the motor cortex received input from both regions, allowing the basal ganglia and cerebellum to overlap their outputs. SMA-proper received projections from both areas, more so from VLo than VPLo, implying a

strong relationship with the basal ganglia in the preparation of sequential movements.

Motorneurons

The motorneurons are represented via the VITE model as described by Bullock and Grossberg (1988). The VITE model is a voluntary movement control system which requires knowledge of the target position, T , and the present position, P , of the joint. A difference vector, V , is used to compute the difference between the target position and the present position at any point in time. In its simplest form, the VITE equations are as follows:

$$\frac{d}{dt}V_i = \alpha(-V_i + T_i - P_i)$$

computes the difference vector with a constant α , and

$$\frac{d}{dt}P_i = G[V_i]^+$$

computes the present position.

In our model of reciprocal aiming, the target position is provided by the motor cortex, where the neuron firing represents the desired joint position. The firing rate of the MC is then correlated with the velocity at which the motorneurons should move. In the VITE model, Bullock and Grossberg used a function to initiate the GO signal. Here, the GO signal is based upon the MC firing rate. In their treatments of the VITE system, Bullock and Grossberg use a scalar value to represent the energy of

the system, and a transfer function, to allow variable speed control and motor priming. Their initial equation,

$$G = G_0 \frac{t^n}{\beta^n + \gamma t^n}$$

where G_0 is the energy of the system, t is the current time, and β , γ , and n are constants. Here, G_0 will be treated as the output strength of the motor cortex. The transfer function is monotonically increasing; thus if G_0 is zero for several timesteps, the transfer function acts as motor priming such that when G_0 becomes nonzero, the muscle is effectively primed to perform a movement. This becomes useful in cases where independent muscles are functioning to perform a coordinated movement where each muscle may start at a different time, but should all end at approximately the same timestep (Bullock & Grossberg, 1989). One of the nice features of the VITE model is that it follows Fitts' Law (Bullock and Grossberg, 1988).

For the reciprocal aiming model, the VITE model must be adjusted to account for several features. First, the VITE model represents only a single muscle, while this model requires a total of six muscles, or a pair of agonist-antagonist muscles for each joint. Second, the VITE model treats each muscle independently of the others; how, then, may the muscles and joints be incorporated so as to behave in a more dependent fashion? ##Need to update the VITE equation to handle this. Do I need the FLETE model for the spinomuscular system? I'm not sure at this stage if it would be helpful. PUP, the third model of the series, is for passive movement of a limb. I do not believe PUP is at all necessary for this experiment, but that VITE is

crucial, and FLETE *may* be helpful. Need to have further discussions with Osman to see if he feels it should be added.##

- Reverse kinematics for the Mns (Jacobian?)
- Do we want forward kinematics of visual input to joint space as information fed to cortex? -- Yes

Model Description

The arm movement is represented via three joints: The elbow joint, for flexion/extension, and two shoulder joints, to allow adduction and abduction in the frontal plane, as well as horizontal adduction/abduction in the transverse plane. The wrist of the model arm is therefore immobile, and tapping a target is translated as tapping the target with one's fingers. These three joints allow for movement within three dimensions, x, y, and z, although for this particular task, only the x and y dimensions are relevant. In order to produce an average behavior across subjects, each trial representing a new subject is given a seed value to represent the height of the individual performing the task. This will affect the kinematics, as in humans there is limb length disparity based upon a person's height. The model treats arm length from shoulder to midline as 0.129H, the length from shoulder to elbow as 0.186H, from elbow to wrist as 0.146H, and from wrist to fingertips as 0.108H, where H is body height (Winter, 1990). A random number generator affecting the velocity component assists in intra-subject variability. {##I think this may be accomplished simply by multiplying a random number by the GO signal. A better approach is to carefully change weight matrices or time constants or other NSL parameters. This is something I need to work on yet.##}

Input to the model is a joint representation of the positions of the two targets via an array, with each element representing a joint angle. This information is first provided to the visually-related neurons of pre-SMA. {##justification/references:see Andy's thesis##}. These neurons project to both PMv and PMd, apprising the premotor areas of the visual stimuli. PMd focuses on the two targets, or stimuli, requiring pairing to a motor program. This information is forwarded to the preparatory neurons of SMA-proper. Through reciprocal connections between pre-SMA and SMA-proper, the sequence of left-right movements is set up. Cross-talk between SMA and PMv completes the construction of the motor program. SMA-proper then informs motor cortex of the movement, so that it may plan to appropriate motor program, and the basal ganglia, so that it may direct the motor cortex and SMA of the overall coordinated control program. The basal ganglia informs SMA as to the current behavior being performed and if it is appropriate to begin preparing/performing the next movement in the sequence.

- ##Note: pictures need to be made **much** prettier for SFN/pubs. I need to decide on a format for them. Dominey's picture structure is an option, although due to the complexity of the diagrams that may be hard to accomplish. Model diagrams would have to be in two parts: one representing cortical connections, the second showing BG/cortical connections, similar to what I did below.##

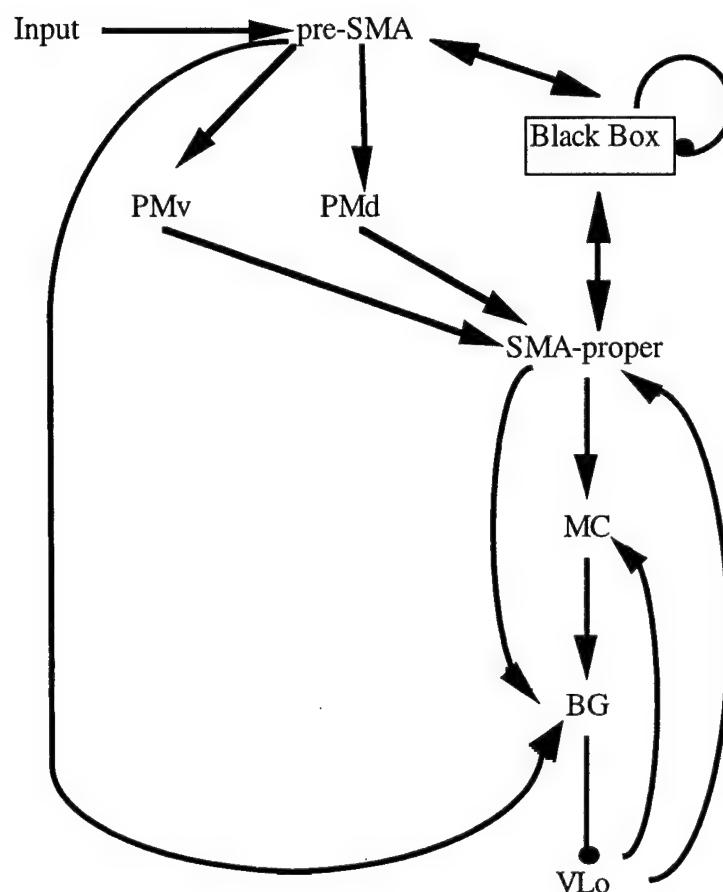


Figure 1. General view of network. Arrows denote positive connections; circles denote negative connections. BG: basal ganglia; MC: motor cortex; PMd: dorsal premotor cortex; PMv: ventral premotor cortex; SMA: supplementary motor area; VLo: ventrolateral pars oralis thalamus.

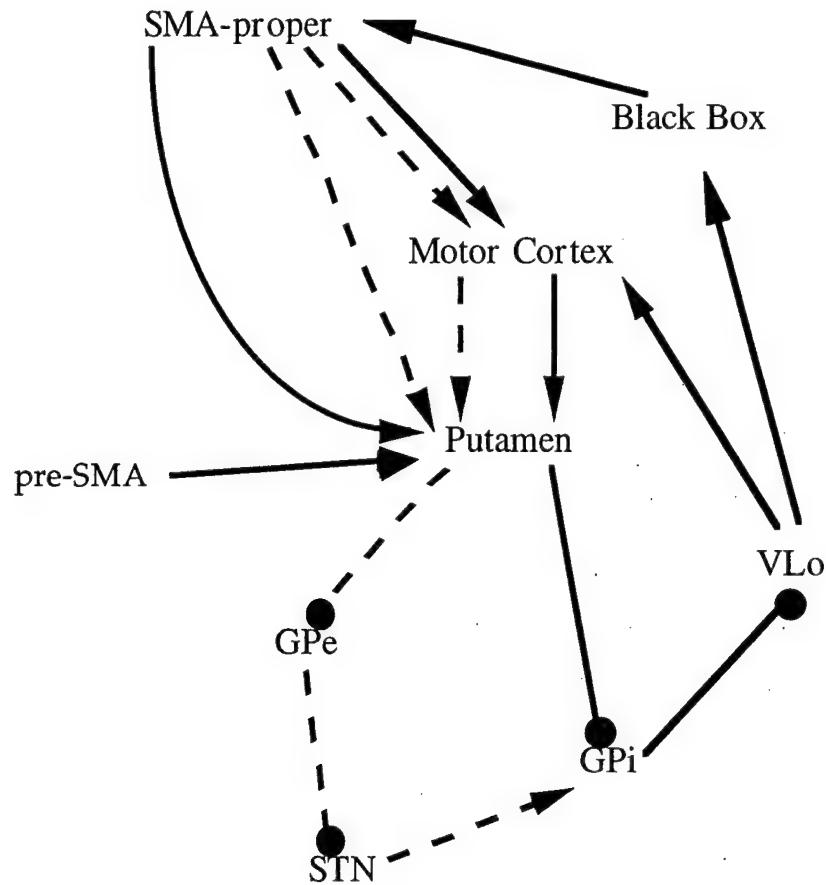


Figure 1. Close-up view of the basal ganglia. Arrows denote positive connections, circles denote negative connections. Solid lines represent movement-related projections, while dashed lines show preparatory/inhibitory connections. GPe: external globus pallidus; GPi: internal globus pallidus; SMA: supplementary motor area; STN: subthalamic nucleus; VLo ventrolateral pars oralis thalamus.

Model Results

The model was implemented in Neural Simulation Language (NSL) (Weitzenfeld, 1991) on a ### workstation. Each brain region is treated as a set of one or more arrays of units, where each array represents a specific neuronal population. In order to simulate the connections between the arrays (brain regions), the following equation is used:

$$\tau_m \frac{dm(t)}{dt} = -m(t) + S_m(t),$$

where $m(t)$ represents an array of membrane potentials of cells of a given type, τ_m is the time constant representing the rate of change for $m(t)$, and $S_m(t)$ represents the total number of inputs of other cells into that particular cell.

- Discuss model results here. Expect to see that for the PD simulations, a slower velocity and more precision due to that factor. Slower velocities may be brought about by changing the time constants in the striatum, since at this point I do not use transmitters, or learning/reward mechanisms of the substantia nigra. This is something to be added at a later stage, more likely for the paper and not for SFN. It may even fall under the update due to synthetic PET results.
- Will show results for: 1) “healthy” subject, 2) “PD” subject, and under predictions, 3) “PD” subject post-pallidotomy to make predictions, but also to compare results to some of Delong’s general PET studies of post-op PDs.

Synthetic PET

Synthetic PET is a technique developed by Arbib et al. (1995) useful in the comparison of modelling data to actual PET studies. The hypothesis is that the cerebral blood flow measured in positron emission tomography (PET) is based upon the synaptic activity of that region; thus, one might compare a neural model which uses computation of synaptic activity in its simulations to an actual PET scan. Given a neural model, one may compute the raw activity $rPET_A$ for region A as

$$rPET_A = \int_{t_0}^{t_1} \sum_B w_{B \rightarrow A}(t) dt$$

where A represents the region of interest, the sum is performed over all regions B which project to region A, $w_{B \rightarrow A}$ represents the activity (firing rate x |synaptic strength|) summed over all the synapses from region B to region A at time t, and integrate over the time interval t_0 to t_1 representing the scan duration. Finally, given the raw activity, one might compare this regional activity between two separate tasks as follows:

$$PET_A(1/2) = \frac{rPET_A(1) - rPET_A(2)}{rPET_A(2)} \times 100$$

- Summarize paper -- see email about formulas
- Discuss synthetic PET of model. How does it compare to a real PET scan, keeping in mind that model is based on primate data?
- From model, I expect to see a decrease in activity in SMA and BG for the PD patients in comparison to the healthy subjects. We may not have real scans of PDs for this part (need to see if Scott can do at Emory, or with Woods at UCLA) but ideally we should try to implement this so that the model may be updated (keeping an eye out for modelling Prablan's perturbed object orientation for normals, with PD results from predictions based on Bennett and Castiello's work on grasp perturbation for PDs and PD sequencing studies) in this paper and make predictions for post-pallidotomy patients. A separate paper could be a comparison model of thalamotomy and pallidotomy! And don't forget the learning aspect to all this!

Model Update

- Discuss how the model is changed to account for the discrepancies between the synthetic PET and the actual PET scan.

Predictions

Recently, there has been a surge in research in the use of surgery to relieve parkinsonian symptoms. One of the more popular treatments, pallidotomy,

involves lesioning of the posteroventral globus pallidus in order to relieve the symptoms of akinesia and rigidity (Ceballos-Baumann et al., 1994; Laitinen, 1995). Pallidotomy may reverse the excessive pallidal inhibition of the thalamus, releasing a Parkinson's disease patient from motor stiffness. Ceballos-Baumann et al. (1994) found in a PET study after right-sided pallidotomy an increase in activation within SMA, lateral premotor cortex, and dorsolateral prefrontal cortex. Since the current model of reciprocal aiming includes only SMA and premotor cortex, it is expected that "lesioning" the pallidal region of the model should produce similar results...

- I plan to model a pallidotomy by effectively lesioning the appropriate GP region of my model, to see if I get results similar to that of Delong's.

Conclusion

Appendix

BG	basal ganglia
GPe	external globus pallidus
GPi	internal globus pallidus
MC	motor cortex
PD	Parkinson's disease
PMd	dorsal premotor cortex
PMv	ventral premotor cortex

SMA	supplementary motor area
STN	subthalamic nucleus
VLo	ventrolateral pars oralis thalamus
VPLo	

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DRAFT

9/30/96

Basal Ganglia Function: Sensory Expectations and the Suppression of Unwanted States

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Abstract

abstract goes here

Introduction

The basal ganglia has received increasing attention over the last decade from both experimentalists and computational modelers in an effort to more fully understand its role in motor control. Alexander and Crutcher (1990a; 1990b; Crutcher & Alexander, 1990) have suggested that the basal ganglia (BG) is involved in the preparation of motor commands and the facilitation of the performance of those commands. Dominey and Arbib (1992) developed a model of saccadic eye movements that used the basal ganglia to control saccade initiation, while Dominey, Arbib, and Joseph (1995) used the BG for selecting and learning an appropriate saccade when multiple saccades are possible. Thach et al. (1993) suggested that the basal ganglia is involved in the inhibition of competing motor programs. Marsden and Obeso (1994) theorized that the basal ganglia may be involved in the permitting of a new cortical motor action, while altering a routine behavior in response to any novel needs. Berns and Sejnowski (1995) proposed two functions for the basal ganglia — it selects an appropriate action from several competing streams of information and, through dopamine, is involved in reinforcement driven learning.

All of these models have the basal ganglia more or less directly involved in the control of movements, either by selecting the motor command to be executed, or through the facilitation of a motor command presumably selected by cortical

mechanisms. However, researchers have found that patients with diseases of the BG, particularly Huntington's disease and Parkinson's disease, do not have significant motor control difficulties when visual input is available (Bronstein & Kennard, 1985; Crawford et al., 1989; Tian et al., 1991), but do have problems with specific forms of internally driven *sequences* of movements ##refs## as well as certain forms of motor memory tasks ##refs##. This implies that the basal ganglia is less involved in the selection of an appropriate motor command, but may instead be involved in assisting cortical planning centers in some fashion as well as in coordinating cross-modal movement timing, e.g., simultaneous arm reach, hand grasp, head movement and eye movement.

We propose that the basal ganglia has at least two primary tasks represented by some complex interplay of its direct and indirect paths (Alexander et al., 1990; Parent & Hazrati, 1993). We suggest that the direct path, involving projections directly from the striatum onto the BG output nuclei, is primarily responsible for providing an estimate of the next sensory state, based upon the current sensory state and the planned motor command, to cortical planning centers. The primary role of the indirect path, where the striatum projects onto the external globus pallidus (GPe), in turn projecting to the subthalamic nucleus (STN), and finally to the BG output structures, is to inhibit motor activity while cortical systems are either determining which motor command to execute, or are waiting for a signal indicating the end of a delay period.

Background

need pictures: diagram of oculomotor, skeletomotor areas, where BG = black box

The Oculomotor Circuit

There are a number of brain regions other than the BG that have been shown to have a role in the generation of saccadic eye movements. We propose the following primary roles for these brain regions in our saccadic eye movement model.

Frontal Eye Fields	Provide the selected saccadic motor signal to the BG and superior colliculus.
Lateral Intraparietal	Provides the potential saccade targets to prefrontal cortex, FEF, and BG.
Prefrontal Cortex	Provides the "go" signal to FEF and BG to begin a saccade and maintains a working memory of saccade sequence order.
Superior Colliculus	Transmits the saccade motor signal to the brainstem to effect a saccade.
Thalamus	Participates in a memory loop with PFC, LIP and FEF and works with the BG to transmit the next sensory state, i.e., estimated next target(s) location, to PFC, FEF and LIP, by spontaneous burst firing under sufficient reduction of BG input.
Brainstem	Controls the position of the eyes.

Frontal Eye Fields

FEF subcortical projections to the caudate nucleus (Alexander et al., 1986) mediodorsal and ventral anterior thalamus (Goldman-Rakic, 1987; Stanton et al., 1988b) and superior colliculus are topographically organized (Stanton et al., 1988a; Stanton et al., 1988b). For some terminal fields, such as those in the intermediate

layers of the SC, the organization of FEF related directly to the collicular map of saccadic amplitudes (Huerta et al., 1986; Leichnetz, 1981; Leichnetz et al., 1984; Stanton et al., 1988b). FEF receives cortical projections from the supplementary eye fields (SEF) (Cavada & Goldman-Rakic, 1989; Huerta & Kaas, 1990; Shook et al., 1990; Shook et al., 1991), lateral intraparietal area (LIP) (Andersen et al., 1985b), and prefrontal cortex (Côté & Crutcher, 1991).

Lateral Intraparietal Cortex

Lateral intraparietal cortex (LIP) has extensive reciprocal connections with the frontal eye fields (Andersen et al., 1985a), the intermediate and deep layers of the superior colliculus (Lynch et al., 1985) and prefrontal cortex. Lesions in LIP resulted in disturbances in visual attention (Mesulam, 1981) and an increase of visually-guided saccade latency (Lynch & McLaren, 1989; Pierrot-Deseilligny et al., 1991) and of memory-guided saccade accuracy and latency (Pierrot-Deseilligny et al., 1991).

Duhamel, Colby, and Goldberg (1992) found immediately before and during a saccade the cortical representation in LIP shifted to the coordinates of the next intended fixation, and then the eye caught up after the completion of the saccade. After the eye movement, the representation in parietal cortex matched the reafferent visual input and the neuron continued to respond to the stimulus.

When monkeys fixated a target (Duhamel et al., 1992) the neurons with the appropriate receptive field fired with a latency of 70 ms. In a saccade task, where the monkey was to saccade to the location of the moved fixation target, the authors presented a visual stimulus that would be in the tested neuron's receptive field upon the completion of the saccade to the moved fixation target. The authors found that the cell began to discharge 80 ms before the beginning of the saccade. Thus, the remapping occurred prior to the initiation of the saccade that brings the stimulus into the receptive field of the cell. Thus, we propose that the remapping found to occur in LIP does not occur through local interconnections as suggested by Dominey

and Arbib (1992), but rather is the result of the next sensory state estimation performed by the basal ganglia.

Prefrontal Cortex

Researchers have shown that the prefrontal cortex (PFC) is crucial for the process of working memory (Boussaoud & Wise, 1993; Goldman-Rakic, 1987; Kojima & Goldman-Rakic, 1984; Sawaguchi & Goldman-Rakic, 1994; Sawaguchi & Goldman-Rakic, 1991). More recent work has been done to show that dopamine, through D1 receptors, plays an important role in this process by participating in the maintenance of internalized visuospatial representations and/or in the control of eye movements governed by these internal cues (Sawaguchi and Goldman-Rakic, 1994; Sawaguchi and Goldman-Rakic, 1991).

Prefrontal cortex has significant reciprocal connections with LIP, FEF and the striatum. In our model we will use prefrontal cortex to provide the trigger signal to BG, LIP, and FEF for when a saccade should be executed. This trigger will cause an increase in the activation of the selected target in LIP and FEF, and a reduction of the inhibition from SNr onto the superior colliculus. The result will be a burst of activity in the superior colliculus to effect the selected saccade.

Superior Colliculus

Cells in the two intermediate and deep layers of the superior colliculus are primarily related to the oculomotor system. These cells receive visual inputs from prestriate, middle temporal, and parietal cortices, and motor input from FEF. Recent theories (Munoz & Wurtz, 1993; Optican, 1994) on saccadic control by the superior colliculus, place it inside a feedback loop. However, two classes of saccade related burst neurons (SRBNs) are utilized. The activity of one class of SRBNs declines sharply during saccades, but the spatial location of this activity remains fixed on the collicular motor map. The spatial activity profile in another class of saccade-related cells, called buildup neurons, expands as a forward progression in the location of its rostral most edge during the saccade. Eventually the expanding

activity reaches fixation neurons in the rostral pole of SC, which become reactivated when the balance between the declining activity of the SRBNs and the fixation cells again tips in favor of the fixation cells. Reactivation of these fixation neurons, which have been hypothesized to inhibit more caudally located burst neurons in the rest of the colliculus in turn functions to terminate the saccade

Keller and Edelman (1994) found that stimulation of the omnipause region in the pons quickly suppressed ongoing saccades and when the stimulation was released, the saccade began again by a resumption of activity in the same SC cells. They also found that when they recorded from SRBNs with less eccentric movements fields that are located anatomically near the midline of the SC (along the rostral-to-caudal axis), there was little or no activity recorded in the same cells during unstimulated saccades with similar amplitudes to the resumed saccades. Taken together, they concluded that this is unequivocal evidence that the population of active SRBNs does not shift on the colliculus during a saccadic eye movement. Further, they also found that the peak saccadic eye velocity during the resumed saccade was lower than the normal saccadic velocity measured in the same animals. Thus, they suggested that the firing rate of the SRBN cells does not code for motor error, but that the peak of the firing serves to deactivate the omnipause cells and initiate the saccade.

Thalamus

Cortical areas PFC, LIP, and FEF receive topographically organized and unique thalamic input from subregions within both mediodorsal (MD) and ventral anterior (VA) regions (Divac et al., 1977; Goldman-Rakic & Porrino, 1985; Kasdon & Jacobson, 1978; Selemon & Goldman-Rakic, 1988). SNr also has significant projections to both MD and VA (Carpenter et al., 1976; Ilinsky et al., 1985; Kultas-Ilinsky & Ilinsky, 1990), and these projections seemed to be the only direct afferent input to the somata and primary dendrites of thalamocortical projection neurons in ventral anterior pars magnocellularis thalamus (VAmc). The cortical afferents that they found were located more distally on the VAmc dendrites. Thus, SNr has a powerful direct

inhibitory connection to the thalamic regions that reciprocally project to FEF, LIP, and the principal sulcus. SNr also has inhibitory projections to the reticular nucleus in the thalamus (Gandia et al., 1993; Pare et al., 1994), and the output of the reticular nucleus is directed to the thalamus, not to the cerebral cortex (Gandia et al., 1993; Jones, 1985; Nauta & Feirtag, 1986). Additionally, Steriade et al. (1986) found that in the awake state, the inhibition of the reticular nucleus onto the thalamus was much stronger on the inhibitory local circuit neurons than on the excitatory thalamic relay neurons. Thus, increased activity in the reticular nucleus would actually result in increased excitability of the thalamocortical relay neurons, instead of increased inhibition.

Based on the above information we model a direct inhibitory topographic projection from SNr to the thalamus to inhibit the current locus of activation representing targets and an indirect excitatory (double inhibition through reticular nucleus) projection from SNr to VA via the reticular nucleus. The reticular nucleus facilitates the growth of activation at the predicted target locations in the thalamus. This thalamic activity projects forward to PFC and LIP where it is used in planning the next saccade prior to the execution of the current saccade. We model the reduction of inhibition for the remapped target location, topographically, in both the reticular nucleus and ventral anterior thalamus. This ensures that SNr does not inhibit the excitatory effects of the reticular nucleus on ventral anterior thalamus (Figure 1).

The Skeleтомotor Circuit

The basal ganglia has a similar role in the generation of movements to that seen in the oculomotor circuit. The cortical regions involved may play the following roles in a model of arm movement:

Premotor Cortex

Involved in visually-guided behavior, and the integration of motor programs.

Supplementary Motor Area Involved in internally-guided tasks, providing information on sequential behavior.

Motor Cortex Generates the force required to move about joints to the desired end position.

Motor Thalamus The link forming a closed loop between cortical regions and the basal ganglia, relaying the inhibition (or lack of) to cortex of forthcoming movements.

Premotor Cortex

The premotor cortex is more related to preparatory behavior (Kurata & Tanji, 1986; Riehle & Requin, 1989). It may be divided into at least two functionally distinct regions: dorsal premotor cortex (PMd), which is involved more in the integration of motor programs needed for the intended action, and ventral premotor cortex (PMv), which appears more specialized for visually-guided execution (Kurata, 1993; Kurata, 1994). The premotor cortex exhibits strong connections to the supplementary motor area, with portions of PMd and rostral PMv connected to SMA-proper, while caudal PMv is linked more strongly to pre-SMA (Luppino et al., 1993). Mushiake et al. (1991) trained monkeys (*macaca fuscata*) to perform a sequential motor task under both visual and internal guidance. While the motor cortex was active in both tasks, the premotor cortex was more stimulated during the visually guided tasks, while SMA was more involved in the internally guided task. Overall, sequence-specific neurons were more common in the supplementary motor area, while transition-related neurons were generally located in the premotor cortex. Both PMd and PMv have regions whose projections reach the internal portion of the globus pallidus (GPi), albeit within different regions (Yoshida et al., 1993). There is also strong evidence that both PMv and PMd receive projections from GPi via the ventrolateral pars oralis region of thalamus (Hoover & Strick, 1993; Inase & Tanji, 1994).

Supplementary Motor Area

The supplementary motor area (SMA) appears to play an important role in motor tasks which require the retrieval of motor memory, as well in the temporal organization and sequential performance of movements (Tanji, 1994). Recently, the SMA has been found to encompass at least two distinct regions, the pre-SMA and SMA-proper (Luppino et al., 1993). SMA-proper has been shown to be a major recipient of pallidothalamic projections, while pre-SMA tends toward cerebellothalamic afferents (Shindo et al., 1995).

Tanji and Shima (1994) recorded from neurons located within SMA-proper of macaques during a sequential task and found a number were active preferentially to a particular order of memory-guided movements. These neurons were not active if the same order was visually guided, or during other sequences. Another group of cells were active between two specific movements, acting rather like a "placeholder," keeping track of the current behavior and in preparation of the next movement of the sequence. Recent studies have shown that pre-SMA is very visual stimulus oriented, rarely responding to somatosensory information, while SMA-proper has more phasic, internally-driven, movement-related activity (Halsband et al., 1994; Tanji & Mushiake, 1996). Pre-SMA also appears to have more "preparatory" activity, receiving massive projections from the frontal cortex, as well as area 46 and PMv. SMA-proper has reciprocal connections with the motor cortex, as well as portions of the premotor cortex and the posterior cingulate. Studies of patients with SMA lesions have also suggested it's involvement in sequential behavior (Halsband et al., 1993).

In comparison, the prefrontal cortex appears to be involved in the learning of new motor sequences. Jenkins et al. (1994) studied the functional anatomy in humans of learning keypress sequences, and found that prefrontal was active only when new sequences were being learned, while the supplementary motor area was more active during performance of a prelearned sequence. Barone and Joseph (1989) also found prefrontal activity in macaques during the performance of spatial

sequencing. However, the monkeys were learning new 3 target sequences for each trial, thus the neural activity recorded may be related to the learning of the sequences. It would be interesting to perform this experiment to the point where the monkeys have overlearned the sequence, in order to compare SMA and prefrontal activities before, during, and after overlearning the sequences. In addition, using auditory or tactile information for direction of sequential seq behavior may be of some value in determining what and how the prefrontal learns sequences. Dominey et al. (1995) modeled a slightly less complex version of the Barone and Joseph paradigm, requiring the learning of the temporal sequence of targets for saccade generation. Here, prefrontal activity increased as the sequences were learned as a result of strengthening the prefrontal-striatal synapses involved in the correct movements.

Motor Cortex

The motor cortex is primarily involved with the performance of movement. Neurons within the arm-hand region are generally restricted to movement about one or two contralateral joints (Humphrey & Tanji, 1991). The pyramidal neurons within the motor cortex group together to form columns which behave as relatively coherent information processing modules (Houk & Wise, 1993). ##MAA: Can you provide us with the Asanuma reference?## These columns may form a loop with the thalamus, such that thalamic neurons receive projections from the same columns to which they project. Most of the corticocortical reciprocal connections are mutually excitatory, with pyramidal neurons sharing information by reinforcing or inhibiting one another. Kalaska et al. (1992) found some neurons demonstrated a load effect. Neurons which were less load sensitive were phasically active before or during a movement, with little posture-related tonic activity. Load-sensitive cells, however, displayed a distinct "phasic tonic" response during movement, involving a short phasic burst followed by a brief pause, and ending with a sustained tonic response while holding over target. Some neurons in MC appeared to be preparatory in nature. Furthermore, they suggested that the motor cortex may transform from the kinematics to the dynamics of reaching movements, which

implies that MC also relies on proprioceptive inputs. In relation to the basal ganglia, the motor cortex may be receiving the expected motor state of the currently planned movement from BG, thus facilitating the linking together of sequential movements.

Thalamus

In primates, the internal globus pallidus projects primarily to the ventrolateral pars oralis region of the thalamus (VLo) (Forlano et al., 1993; Vitek et al., 1994). The thalamus contains primarily relay neurons, acting as a gateway which filter the flow of information to the cortex (Jones, 1985; Sherman & Koch, 1990). VLo projects to SMA-proper (Rouiller et al., 1994), as well as to at least the hand region of the motor cortex (Holsapple et al., 1991). VLo may therefore be useful in assisting the basal ganglia to signal SMA to prepare or execute the next movement in a sequence. The ventralis oralis posterior (Vop) and ventralis intermedius (Vim) neurons in man (VLo in primates) show large tremor frequency activity which has been correlated with parkinsonian tremor (Lenz et al., 1993). MPTP-treated monkeys demonstrated an increase in tonic activity in GPi, as well as abnormal bursting activity related to tremor. Therefore, with the thalamus acting as a relay to the cortex, the GPi bursts may ultimately project their bursts to motor cortex, producing parkinsonian tremor (Lenz et al., 1993).

Conceptual Model of the Basal Ganglia

Does the basal ganglia prepare movements, or is it simply inhibiting undesired motor programs from being enacted? Does it select a "motor program" based on its cortical input, or is it involved, as we believe, with providing cortical planning centers a preview of the sensory and motor state that will exist after the currently planned motor command executes? We propose that the overall role of the basal ganglia is twofold: first, it acts as a feedforward mechanism, providing next sensory state information to the cortex, such that the next movement may be planned while the current movement is in progress; second, it is involved with the inhibition and

timing of movements across all motor control domains. Next sensory state information may be part of what is lost in Parkinson's disease patients: without knowledge of the next state, the supplementary motor area (SMA) and prefrontal cortex (PFC) may have difficulty in planning the timing of the next movement to perform, thus exhibiting the pause seen between movements within a sequence (Bennett et al., 1995; Castiello & Bennett, 1994). In Huntington's disease, the reduction of tonic BG inhibition may account for chorea and involuntary movement.

The striatum receives the majority of the input to the basal ganglia. Its primary output neurons are GABAergic and project to the output regions of the BG — the substantia nigra pars reticulata (SNr) and the internal globus pallidus (GPi) — as well as to the external globus pallidus (GPe). The external globus pallidus has inhibitory, tonically active, GABAergic neurons which project to the subthalamic nucleus (STN). The subthalamic nucleus (STN) receives excitatory input from the motor and somatomotor cortical areas, as well as tonic inhibitory input from GPe. Output projections of STN are glutamatergic and excitatory, and most project to the SNr and GPi. SNr/GPi project primarily to the thalamus, but they also project to the superior colliculus and pedunculo pontine nucleus. The GABAergic neurons of GPi and SNr are tonically active neurons that provide an inhibitory signal to the regions to which they project. Inhibitory striatal activity through the direct path reduces the inhibitory output of the BG, thus decreasing its inhibition upon the regions to which they project. Whereas, activity in the indirect path, whether through the inhibition of the striatum onto GPe and then onto STN, or whether through direct cortical stimulation of STN, increases the inhibitory output of the BG.

If, as we propose, the direct path is primarily responsible for the remapping to new sensory locations and the indirect path is primarily responsible for inhibition of the currently planned motor command, then there must be a certain level of separation between the inputs to these paths. Le Moine and Block (1995), using an improved *in situ* hybridization technique, studied D1 and D2 receptor genes within

the caudate-putamen and nucleus accumbens in adult rats. They found distinct, with only slight overlap, populations of D1 receptor genes in GABA/substance P striatonigral projecting neurons and D2 receptor genes in GABA/enkephalin striatopallidal projecting neurons. This supports previous *situ* hybridization studies (Gerfen et al., 1990; Le Moine et al., 1991; Le Moine et al., 1990), as well as pharmacological and anatomical studies in rats using retrograde tracing and lesioning of the striatonigral or striatopallidal pathways (Harrison et al., 1990; Harrison et al., 1992; Pollak et al., 1993; Schiffman & Vanderhaegen, 1993) and receptor binding studies (Beckstead, 1988; Richfield et al., 1989). Additionally, striatopallidal projection neurons within the striatal matrix typically project exclusively to either GPe (about 70%) or to the internal globus pallidus (30%), and only rarely to both regions (Flaherty & Graybiel, 1993). Other researchers have found that the movement-related cortical regions (MC, APA) have more influence over the direct pathway (GPi), while the preparatory-related regions (SMA-cingulate, premotor cortex (PM)) preferentially project to GPe and the indirect pathway (Nambu et al., 1990; Yoshida et al., 1993).

The subthalamic nucleus receives excitatory direct input from motor and somatomotor cortical areas (Afsharpour, 1985; Canteras et al., 1990; Nambu et al., 1996), as well as tonically inhibitory input from the striatum through the external globus pallidus (GPe). The motor cortex projects mainly to lateral STN, while the supplementary motor area projects mainly to medial STN (Nambu et al., 1996). These cortical regions rarely project to ventral STN, to which the oculomotor-related regions (frontal eye field and supplementary eye field) project strongly (Huerta and Kaas, 1990). Additionally, the dorsal aspects of STN project to the putamen, and hence contribute to somatic motor function, while the ventral aspect projects to the caudate. Ryan and Clark (1992) found that large lesions of the globus pallidus increased the response of the STN to cortical stimulation in three ways: increased number of STN neurons firing, increased duration of evoked response, and increased firing rate. Partial lesions of the globus pallidus resulted in only a portion of STN cells showing this exaggerated response. This data supports the

view that the STN is subdivided into topographically organized subregions. In further support of this view, Wichmann et al. (1994) found an anterodorsal sensorimotor region and a caudoventral area not related to body movements. The motor region was further subdivided into regions whose activity was related to the movements of specific body parts. Given these projections, and the additional fact that the SMA projections are mirror-images to the MC projections (Figure 2), the variations of hemiballism may be explained. For example, lesions within the mediolateral central zone of STN may affect the leg projections from both SMA and MC, while lesions comprising part of or the entire mediolateral extent would affect forelimb and/or facial zones of both MC and SMA (Nambu et al., 1996).

Hikosaka et al. (1993) found visuo-oculomotor cells in ventral STN. They classified the task-related activities into four types: saccadic, visual, fixation, and others. They frequently saw sustained activity during visual fixation in STN. The activity began when the monkey started fixating a central spot and continued until the end of the trial, except when a saccade was made to a target. The activity occurred independent of the target direction. The authors suggest that the activity is not a short-term memory, but that this activity is used to suppress an upcoming movement. This provides direct support for our proposal that the indirect path is primarily involved in motor command inhibition during delay periods and releases this inhibition when a cortically-provided go signal is received.

Another issue to be addressed by our model involves the remapping of the current state of sensory and motor signals into an estimation of the future state of sensory inputs based upon the execution of the planned motor command. We propose that the BG is only able to remap sensory/motor state combinations that it has previously learned through repetition. It is this remapping that allows the BG to improve the performance of sequential movements and has minimal effect on single movements. To be able to remap a visual target from one location to another location based upon a specific eye movement requires neuronal interconnections supporting this growth of activity in a new location. We propose that the patchy projection patterns seen in the striatum from afferent cortical connections is the

basis for this remapping by dividing a sensory or motor input into a number of distinct locations. In fact, cortical projections from even small regions of the cortex project to the BG as a discontinuous set of patches (Flaherty & Graybiel, 1991a; Flaherty & Graybiel, 1994; Selemon & Goldman-Rakic, 1985). Other experiments have shown that corresponding cortical sites that are not heavily interconnected can still send convergent projections to the striatum (Flaherty & Graybiel, 1991b; Jones et al., 1978).

The difficulty that arises from this patchy, distributed association network in the striatum is how to funnel the information back to cortical areas such that they can utilize the result of the BG activity. Percheron et al. (1984) performed anatomical studies that suggested widely separated striatal neurons may converge on the same pallidal dendrites. Gimenez-Amaya and Graybiel (1990; 1991) using retrograde tracers in GPe and GPi, found clusters and bands of labeled neurons in the striatum. Flaherty and Graybiel (1994) found multiple striatal matrisomes labeled by retrograde tracers from single sites in both GPe and GPi that all received inputs from single body-part representations in sensorimotor cortex (SI and MI). This data shows that clusters of widely spaced neurons in the striatum project to small areas in the output nuclei of the BG and could form the basis for remapping a sensory signal to a new location. However, one last requirement for remapping must be that small populations of neurons in the striatum can project to multiple locations in SNr/GPi which would allow different combinations of sensory and motor input to map to different sensory locations. This type of striatal connectivity with GPi/SNr has been demonstrated by several researchers (Gerfen, 1985; Haber et al., 1990; Hedreen & DeLong, 1991). Thus, small regions from cortex project to a number of discontinuous regions in striatum and different cortical regions containing similar sensory/motor information, e.g., visual information and eye movement commands, project to overlapping regions. Additionally, small regions in the striatum project to a number of regions in GPi/SNr and multiple regions in striatum project to small regions in GPi/SNr. Figure 3 shows this type of connectivity schematically.

Besides the interesting anatomical connectivity of the BG, there are a number of neuromodulators present in the striatum, with dopamine seeming to play the dominant role. The dopaminergic neurons of the substantia nigra pars compacta (SNc) project to the striatum, and appear to have a modulatory effect on the direct and indirect pathways of the basal ganglia. We propose that dopamine is not only required to learn the sensory/motor state remappings, but is also needed to express the learned relationships. To this end, we review data on when the dopaminergic neurons in SNc become active and the striatal changes that occur with the presence of dopamine.

Schultz and his coworkers (Ljungberg et al., 1992; Mirenowicz & Schultz, 1994; Schultz et al., 1993a; Schultz et al., 1993b) have found three conditions that cause dopamine cells within the substantia nigra pars compacta to fire: novel stimuli, primary rewards (e.g., food or juice), and conditioned stimuli known to indicate the arrival of a primary reward. Others have found that dopamine neurons are not necessarily activated in relation to specific motor commands (DeLong et al., 1983; Schultz et al., 1983), nor do dopamine neurons continue to fire during delay periods (Ljungberg et al., 1991; Schultz & Jromo, 1990). From this data, Schultz (1992) proposed that dopamine neurons signal the presence of an important stimulus, without specifying specific details of what is to be accomplished. Calabresi et al. (Calabresi et al., 1992a; 1992b) have shown that repetitive activation of cortical inputs produces LTD in striatal cells whose NMDA channels are inactive and long-term potentiation (LTP) in those whose NMDA channels are active. Thus, similar to Rosenblatt's perceptron (Rosenblatt, 1962), dopamine could strengthen local associations that support a correct, or near correct output, and weaken inappropriate associations.

Dopamine also seems to affect the large aspiny interneurons in the striatum. Kimura, Aosaki, and Graybiel (1993) found that the number of tonically active neurons (TANs) in both caudate and putamen firing in response to the performance of a task gradually increased from 10-20% to 60-70% once the task was learned. They also found that the TANs developed a pause in their firing often flanked by short

excitatory pulses. This pause occurred shortly after the conditioned stimulus was presented and recent evidence (Aosaki et al., 1995) has shown that these neurons become temporally coordinated across large regions of the striatum during sensorimotor learning. When the monkeys were given extinction training, this pause response diminished and eventually disappeared. When Kimura et al. (1993) removed the supply of dopamine via the injection of MPTP, the number of TANs firing was reduced to the unlearned levels in caudate. They found that the response rate to the conditioned stimulus recovered when they injected the dopamine agonist apomorphine; however, response rates of dopamine-depleted TANs did not increase even during three months of additional training. Lastly, they found that these TANs, though only a small percentage of the number of neurons in the striatum, tend to lie along the striosome/matrix borders (Aosaki et al., 1995). Thus, many of these neurons are in a position to communicate a primary reward signal, e.g., food or juice, from the striosomes, carried via dopamine, to the surrounding matrix containing medium spiny projections neurons which synapse onto the output structures in the basal ganglia. This signal would then be used to facilitate the execution of motor behaviors selected by higher cortical centers involved in motor planning.

Another method by which we can evaluate the role of the basal ganglia in motor control is to monitor the effects of BG diseases upon motor control and motor planning. Parkinson's disease and Huntington's disease are two BG disease with a large body of available literature. In PD, the dopaminergic neurons in the substantia nigra pars compacta die, with a resulting decrease of dopamine in the striatum. Huntington's disease is an inherited, autosomal dominant degeneration of specific classes of cholinergic and GABAergic neurons primarily in the striatum (Martin & Gusella, 1986).

Parkinson's disease patients seem to display difficulties both in sequential execution of multiple motor "programs" as well as in motor planning. Bennett et al. (1995) requested control subjects and Parkinson's disease patients to reach 28 cm to a half-filled cup of water, grasp it, and then take a sip of water ("reach-grasp" and

"take-to-lips" tasks). Eight of nine PD patients exhibited a pause (average 340ms) between these two tasks during at least one trial, though none of the controls displayed a pause. The pause was unrelated to the subject's age, sex, or disease severity, nor was it related to a lower or higher movement initiation time, and therefore unlikely due to insufficient or prolonged planning. In another experiment, Castiello and Bennett (1994) asked PDs to reach and grasp either a small cylinder, where a precision grip was more appropriate, or a large cylinder, where a whole hand grasp was more appropriate. Occasionally, at the onset of movement, the cylinder was switched. When PD patients were permitted to choose a grasp, there was a plateau between grasp type transitions, which was not displayed by the control group. The mean duration of the plateau was 398 ms, or 28% of the total movement duration. This plateau is similar to the pause found in the previous experiment where switching between motor programs is involved. This data supports the hypothesis that the basal ganglia may be involved in some manner in smooth transitions between sequential movements.

PDs also appear to demonstrate a deficit in planning (Morris et al., 1988). In the Tower of London test (similar to the Tower of Hanoi, subjects were required to move colored beads among three upright poles to match a given pattern). While both the Parkinson's patients and controls showed some increase in the planning times as puzzle difficulty increased, the planning time was much longer for PDs than for the controls. This suggests an impairment of internal control in sequence planning. When the same subjects were shown a short sequence of spatial moves to memorize for later execution, they performed as well as the control subjects, suggesting that spatial short term memory is unimpaired.

Huntington's disease patients show greater defects in initiating internally generated saccades than in generating externally triggered saccades (Willingham & Koroshetz, 1993). Tian et al. (1991) found that HD patients were less able to anticipate the timing and location of a visual target that predictably alternated its position than were control subjects. Others have shown that HD patients have a greater latency for voluntary saccades than for reflexive saccades, that they have

difficulty in inhibiting saccades to suddenly appearing objects and in performing anti-saccades (Bollen et al., 1986; Lasker et al., 1987; Lasker et al., 1988; Leigh et al., 1983; Sprengelmeyer et al., 1995). Sprengelmeyer et al. (Sprengelmeyer et al., 1995) found that HD patients are not impaired in reacting to external stimuli, but do have difficulties in monitoring both auditory and visual information channels simultaneously and in using this multi-modal information effectively in formulating the correct response in the experiment.

Conclusion

Parkinson's disease and Huntington's disease patients show a slowness in movement and difficulties in learning sequential movements as well as control subjects (Agostino et al., 1992; Benecke et al., 1987; Harrington & Haaland, 1991), however, patients are able to perform the correct movements, only the timing and speed with which the movement is performed seems to be affected. Thus, we suggest that the BG is less involved with the *selection* of the correct motor program, since the loss of BG should then produce a deficiency in the selection of the correct motor program, but instead is providing estimates of the next sensory state, based on the currently selected motor program, through implicit learning of previously presented sequential tasks. Thus, a decrease in the performance of the BG does not cause incorrect motor program selection, but instead forces cortical motor planning centers to execute movements independently. Therefore, each individual movement is correct (though movement dynamics may differ from normals), but the coordination of movement sequences is lost, or disrupted.

We also propose that another function of the basal ganglia is to inhibit currently planned motor programs from being executed until a cortically-initiated "go" signal is received. We have discussed data showing that there are topographically-organized, fixation-related neurons in STN that receive direct projections from the cortex (Afsharpour, 1985; Canteras et al., 1990; Nambu et al., 1996) and that the preparatory-related regions (SMA-cingulate, premotor cortex (PM)) preferentially project to GPe and the indirect pathway (Nambu et al., 1990; Yoshida et al., 1993).

Additionally, Hikosaka et al. (1993) frequently saw sustained activity, independent of target direction, during visual fixation in STN that began when the monkey started fixating a central spot and continued until the end of the trial, except when a saccade was made to a target.

The question then is why should the basal ganglia have responsibility for two seemingly disparate functions? We propose that in order for the BG to pass its next sensory state estimate to the cortex at the proper time, it must know when these same regions have completed their planning for the next motor command to be executed. Thus, the cortical go signal which initiates the release of the BG inhibition on the currently selected motor command also provides the go signal for the BG to pass its next sensory state prediction to cortical planning centers. By linking the inhibition of motor commands while planning is in process with a mechanism providing advance information on a future sensory state in the BG, the brain has ensured that the timing of the two activities is correlated. Thus, planning for the second movement in a sequence does not begin before the motor program for the first movement has been passed to the circuitry that carries out the movement.

If the two tasks are interrelated as we believe, then it may be difficult to define experiments that can test the two tasks independently. For instance, lesioning the direct cortical projections to STN should impact the ability of the basal ganglia to inhibit motor commands prior to receiving a cortical go signal. However, the increased distractibility that should result would also affect the remapping task in BG, as either the wrong motor command would be executed prior to the correct motor command, e.g., antisaccade tasks in Huntington's disease (Lasker et al., 1987; Lueck et al., 1990), or the timing of motor command execution and next sensory state prediction would be disrupted. Another experiment would be to make a small lesion between SNr and thalamus, or between thalamus and LIP. The lesioned projections should not be able to convey the next sensory state signal, where nonlesioned projections should function normally. Thus, the growth in activity seen by Duhamel et al. (1992) of target memories to the remapped site should not be seen.

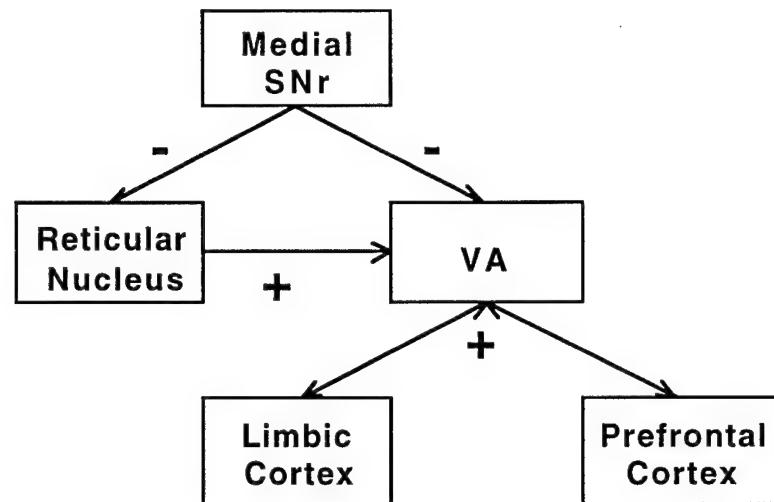


Figure 1a - Motor Command Inhibition Circuit

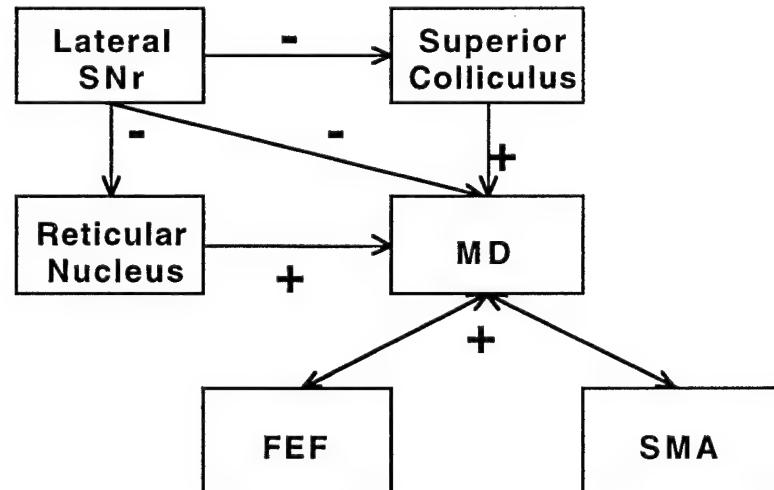


Figure 1b - Next Sensory State Estimator Circuit

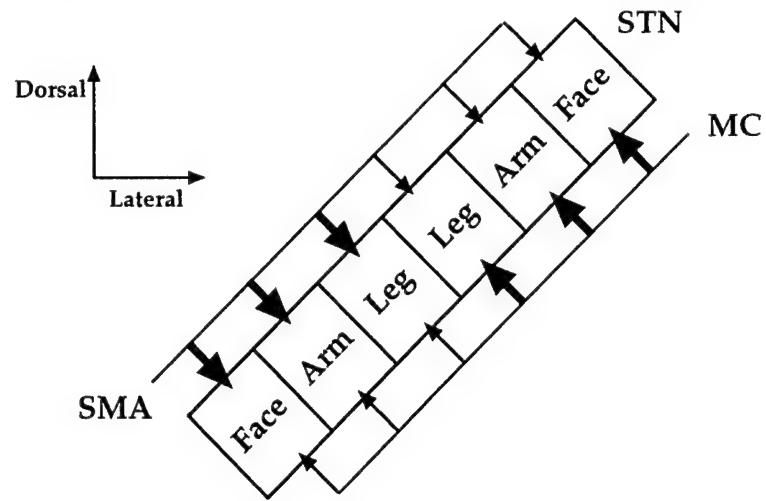


Figure 2. Diagram of projections of motor cortex and supplementary motor area to the subthalamic nucleus. MC: motor cortex; SMA: supplementary motor area; STN: subthalamic nucleus. Adapted from Nambu et al. (1996).

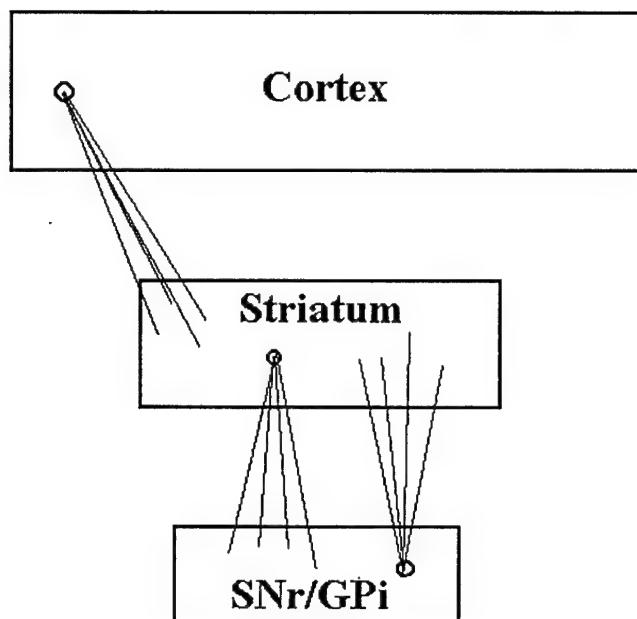


Figure 3. Update picture, write text.

Abbreviations

APA	arcuate premotor area
BG	basal ganglia
CVLT	California Verbal Learning Test
DA	dopamine
FEF	frontal eye fields
GABA	???
GP	globus pallidus
GPe	external globus pallidus
GPi	internal globus pallidus
HD	Huntington's disease
HRP	horseradish peroxidase
LIP	lateral intraparietal area
MC	motor cortex
MD	mediodorsal thalamus
MPTP	???
MSN	medium spiny neuron
NAc	???

OCD	obsessive-compulsive disorder
OFC	orbitofrontal cortex
PD	Parkinson's disease
PET	positronic emission tomography
PFC	prefrontal cortex
PM	premotor cortex
PMd	dorsal premotor cortex
PMv	ventral premotor cortex
SC	superior colliculus
SEF	supplementary eye fields
SI	somatosensory cortex
SMA	supplementary motor area
SRBN	burst neuron
STN	subthalamic nucleus
VA	ventral anterior thalamus
VAmc	ventral anterior pars magnocellularis thalamus
Vim	ventralis intermedius thalamus
VLo	ventrolateral thalamus pars oralis
Vop	ventralis oralis posterior thalamus

VPLo ventral posterolateral pars oralis thalamus

VTA ventral tegmental area

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